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Pheo or Not a Pheo, That Is the Question

THE ADRENAL GLANDS have fascinated physicians over the centuries. The first anatomist to give a detailed description of the human adrenal glands was Eustachius in the 16th century, but his observations were unpublished for some time.[1] Surprisingly, the adrenal glands were described as hollow by Bartholin in the 17th century. This concept was corrected in the 19th century when it was clearly recognized that the adrenal glands were solid structures and that there were two portions of the adrenal gland, the cortex and the medulla. The advent of microscopy and histochemistry provided definitive proof that the medulla was a distinct part of the adrenal gland. The chromaffin reaction, a brownish deposit in the adrenal medulla after the fixation of catecholamines in chromic acid, or dichromate salts, was described in the middle of the 19th century. Epinephrine was among the earliest hormones discovered and was isolated in crystalline form and the chemical structure elucidated in 1897. It was synthesized in 1904 and later was shown to be present in increased amounts in patients with pheochromocytoma.

In 1886 Fränkel described the case of a young woman with the symptoms of a pheochromocytoma in whom, at autopsy, bilateral adrenal tumors were found. In 1922 Labbé reported a case and was the first to attribute the symptoms to the adrenal tumors. The next year, Professor Villard of Lyon operated on a patient who died in shock. In 1926 C. H. Mayo at the Mayo Clinic and G. Roux in Switzerland successfully removed adrenal tumors and dramatically reversed hypertensive episodes.

Over the midportion of the 20th century, the identification of norepinephrine, dopamine, other precursors, and metabolites led to rapid advances in the biochemical diagnosis of pheochromocytoma. Precision in the measurement of these compounds was further refined by high-pressure liquid chromatography and radioisotopic labeling techniques, which have substantially contributed to the preoperative diagnosis and follow-up in patients with catecholamine-producing tumors. The development of scanning techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), as well as radioisotopic (iodine 131) labeling of *m*-iodobenzylguanidine (MIBG), has greatly contributed to the preoperative localization of tumors. The recognition of the significance of abnormal DNA ploidy, that is, that this is associated with the potential for malignancy, has considerably improved patient care and follow-up.

Pheochromocytoma is a rare tumor that can occur at any age, but the peak incidence is in the fourth through the sixth decades. Among the general population of Olmsted County, Minnesota, the incidence of pheochromocytoma is 9.5 per million population per year, in the Netherlands 0.4, Denmark 1.9, and Sweden 2.1. These rates vary, largely related to the acquisition of the material, both clinically and at autopsy. The incidence of pheochromocytoma among hypertensive persons has decreased greatly, largely because essential hypertension has been diagnosed in more people in recent years as the blood pressure limit for normal has been lowered. For example, from 1973 to 1975, the annual incidence of pheochromocytoma at the Mayo Clinic was estimated to be 0.4 per 1,000 hypertensive persons with diastolic pressures of 95 mm of mercury or more. Pheochromocytoma continues to be a diagnostic challenge as a substantial proportion of cases of pheochromocytoma found at autopsy are still undiagnosed clinically.

Pheochromocytoma may be part of a polyglandular endocrine derangement or may be associated with other neuroectodermal disorders. There is an increased incidence in families, particularly when the index case is a child with pheochromocytoma and also when pheochromocytoma is present in both adrenal glands. Autosomal dominant inheritance is seen in persons with multiple endocrine neoplasia (MEN) type II, in association with pancreatic islet cell tumors, and in neuroectodermal disorders (such as neurofibromatosis and von Hippel-Lindau disease). Families with multiple adrenal and extra-adrenal pheochromocytomas unassociated with other tumors or syndromes also have been reported. The Carney multiple neoplasia triad of extra-adrenal paragangliomas, gastric leiomyosarcomas, and pulmonary chondromas is a rare but interesting triad of rare tumors that is not familial. Almost all of the reported Carney cases have been in young women, and the finding of any two components of this triad should raise serious consideration of this syndrome.[2]

Pheochromocytoma is not caused by a single genetic defect. The genetic locus for this tumor has been attributed to chromosome 10 for MEN II, chromosome 17q for neurofibromatosis type I, chromosome 22 for neurofibromatosis type II, and chromosome 3p for von Hippel-Lindau disease. In nonfamilial cases, several genetic locations have been attributed.

Pheochromocytoma arises from chromaffin cells that are located in the adrenal medulla, but also in paragangliomas, which may be located anywhere from the base of the brain—such as the glomus jugulare—to the testicle, including the mediastinum and inside the heart arising from the interatrial cardiac septum and within the myocardium itself. Most (90%) pheochromocytomas arise in the adrenal medulla, and most of the extra-adrenal tumors also occur in the abdomen. This information is helpful when planning imaging studies.

Malignancy is more frequent in extra-adrenal tumors and when tumors arise in young persons. The incidence ranges from 3% to 14%. Nuclear DNA-ploidy studies by flow cytometry have shown that patients with a normal DNA histogram follow a benign course, whereas 30% to 40% of the remainder have or develop evidence of malignant disease in follow-up studies.[3]

In the article on pheochromocytoma elsewhere in this issue of the journal,[4] Philip Cryer, MD, describes the physiology of the sympathochromaffin system and notes the potential of the cells to produce a vast array of peptides and other compounds.[2] The biologic action of these compounds in contributing to the symptoms of pheochromocytoma, in addition to the symptoms attributable to catecholamines, is unclear. While paroxysms of hypertension are by far the most com-

ABBREVIATIONS USED IN TEXT

CT = computed tomography
MEN = multiple endocrine neoplasia
MIBG = *m*-iodobenzylguanidine
MRI = magnetic resonance imaging
VMA = vanillylmandelic acid

mon clinical symptom, occasionally pheochromocytomas may be asymptomatic and are found serendipitously. In other rare instances, hypotension and polyuria are prominent in patients whose tumors produce predominantly epinephrine or dopamine. On occasion, the erratic blood pressures are clearly shown on ambulatory blood pressure monitoring where both symptomatic and asymptomatic paroxysms of hypertension and orthostatic hypotension can be demonstrated. While not diagnostic, this pattern suggests the diagnosis.[5]

Although the family history, the symptoms, and the findings of a physical examination may give clues to the presence of one of the heritable syndromes and to sporadic pheochromocytoma, the diagnosis must be made on the biochemical determination of the excess production of catecholamines and metabolites. In rare instances, totally asymptomatic and biochemically negative tumors may be found, but almost always when these patients are operated on, manipulation of these tumors causes cardiovascular crises. Computed tomographically guided needle biopsies of pheochromocytoma in the absence of α- and β-adrenergic blockade—as in the preparation for any surgical procedure in these patients—can be hazardous.

The question of which test or tests to use in screening is not an easy one to answer.[6,7] Any single test chosen may be negative on occasion, but most are positive in all patients. Given an excellent biochemical technique for measuring the particular substance, the decision then comes down to practice style. When a well-measured 24-hour urine specimen can be obtained, the measurement of metanephrine excretion is the least invasive and most economic screening test. A measurement of vanillylmandelic acid (VMA) levels is almost as good. In any case, an abnormal screening test result should be confirmed by all three tests: fractionated free catecholamines, metanephrines, and VMA. A well-timed urine collection of less than 24 hours' duration, related to creatinine concentration, can also be used; it is thought that an overnight collection is best because of the reduced sympathetic activity during sleep, and thus an autonomous hypersecretion of catecholamines can be measured more readily. Plasma catecholamine levels are useful in confirming the diagnosis when the specimen is obtained under carefully controlled circumstances, as described in Cryer's article.[2] There can be great biologic variation and marked changes in plasma catecholamine levels under many physiologic and nonpheochromocytoma situations. It is important to reiterate that the specimens for measuring plasma catecholamine levels are best drawn with an indwelling catheter in a basal state. When doing biochemical tests, it is important to recognize the physiologic and other circumstances that can interfere with the interpretation of the test. In addition, specific interference—such as the presence of methylglucamine, a component of many iodine-containing contrast mediums—will falsely lower metanephrine levels for as long as 72 hours after its use parenterally; methenamine mandelate consumes catecholamines within the urinary bladder; clofibrate can reduce the concentration of VMA in the urine. Labetalol hydrochloride, a drug commonly used to manage pheochromocytoma, can interfere with *all* of the biochemical determinations.[4] It is rarely necessary to use pharmacologic tests, but, if desired, provocative tests using histamine, glucagon, and metoclopramide and a suppressive test with clonidine could be considered.

After the diagnosis has been considered clinically and confirmed biochemically, preoperative localization should be attempted because of the many locations in which a functioning pheochromocytoma may be found. Magnetic resonance imaging will likely become the preferred technique as it becomes more universally available. It identifies the adrenal lesions as well as CT but is better for extra-adrenal tumors. Magnetic resonance imaging does not require the administration of any glucagon or contrast media, which can provoke a catecholamine crisis, unless the patient is protected with α- and β-adrenergic blockade. Scintigraphy has not proved to be as useful as other imaging procedures in the initial evaluation of patients, although the entire body can be imaged. There is a 10% to 20% false-negative rate. Labetalol use and that of many other compounds interfere with the uptake of the isotope by catecholamine-containing cells.[8] At the Mayo Clinic, with sporadic cases of pheochromocytoma, when CT of the adrenal areas, the rest of the abdomen, and the pelvis is negative, [^{131}I]MIBG scintigraphy directs the next location to image with MRI. Scintigraphy using [^{131}I]MIBG has an important place in the evaluation of familial cases in patients in whom the presence of metastases, multiple tumors, or extra-adrenal tumors or malignancy is being considered. For example, we recently saw a patient in whom [^{131}I]MIBG scintigraphy located a metastasis behind the left clavicle following a normal CT examination of the chest and abdomen. This was clearly shown on MRI.

Preparing a patient for the surgical excision of a pheochromocytoma is as critical as the operation itself. The effects of catecholamine storms on the body can be prevented by appropriate adrenergic receptor blockade. α-Blockade is initiated until the patient is normotensive with slight orthostatic hypotension. Oral fluid and sodium loading restores the intravascular volume. β-Blockers are added for three days before the operation in almost all patients unless there is cardiomyopathy present. α-β-Blockers such as labetalol can be successfully used in many patients, but individual patients may not respond as well as to α- and β-blocking drugs administered separately in full doses. In a patient who does not respond as well as expected to adrenoreceptor blockade, consideration should be given to using converting enzyme inhibitors because renin levels are often elevated in these patients; sometimes this is due to inadequate volume repletion at the same time as the adrenoreceptor blockade is being initiated. Calcium channel blockers or the rate-limiting enzyme inhibitor, metyrosine, can be considered also. During the operation, blood pressure and arrhythmia monitoring and control are imperative, and the use of intravenous sodium nitroprusside is routine. Other parenteral drugs that can be used include labetalol, nicardipine hydrochloride, nitroglycerin, phentolamine mesylate, adenosine, and esmolol hydrochloride. As indicated by Cryer, a postoperative urine collection for catecholamine and metabolite analyses a week or longer after the operation is an essential part of the management to be certain that all of the abnormalities have resolved and that

there is no residual functioning tumor. DNA ploidy of the tumors should be measured and assigned the highest grade of several specimens. When DNA is normal, follow-up can be limited to repeating biochemical tests if symptoms recur. For those with abnormal ploidy, annual biochemical studies, such as 24-hour urine collections by mail, should be carried out indefinitely because the malignancy rate may be as high as 30% to 40%.

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Congenital Heart Disease—The First Test

IN THIS ISSUE of the journal, one of the deans of pediatric cardiology tells of the history and physical examination clues in diagnosing congenital heart disease.[1] Arthur J. Moss, MD, Emeritus Professor and former chair of the Department of Pediatrics at the UCLA School of Medicine, has long championed the clinical diagnosis of heart disease in children. In this high-tech world, that approach may seem out of favor. Now, with cost containment being an ever-increasing issue, it is well that attention be paid to the diagnostic pearls of an acknowledged pioneer and expert in diagnosing children's heart defects.

The history and physical examination should be regarded as the number one noninvasive test to be applied in making cardiac diagnoses. Yet, it is not uncommon for providers of primary childhood health care to do an echocardiogram when the question of heart disease arises. Despite its accuracy when expertly done, this is an expensive test. In addition, the echocardiogram is often done in a community hospital setting by a technician who does the test on one or two children and a few infants each month. The recorded tape may be sent to a center where the reading pediatric echocardiographer does not see the needed views and ends up reporting that "clinical correlation is necessary." In contrast, applying the clues described by Moss may obviate the need for further testing. At the very least, these historical and physical clues make intelligent referral possible and save thousands of dollars.

As noted by Moss, the age at which a cardiac diagnosis is suspected influences diagnostic possibilities. In the newborn, most often the discovery of cyanosis, respiratory difficulty, or a heart murmur leads to the consideration of a heart disorder. If all three coexist, the likelihood of heart disease is great. In this setting the respiratory distress equates to heart failure. In the first week of life, heart failure is most often caused by a transposition of the great arteries, the coarctation syndrome, or a hypoplastic left ventricle. Persistent truncus arteriosus may be added to the list. All of these defects may have associated cyanosis or at least decreased arterial oxygen saturation. All are treatable by surgical intervention in early life. Thus, respiratory distress in the first days of life, when thought to be due to a heart defect, requires pediatric cardiac consultation, not an echocardiogram.

On the other hand, neither cyanosis nor the presence of a heart murmur necessarily means that a heart defect is present. The need to distinguish central from peripheral cyanosis in a newborn infant is well discussed by Moss. As noted, cyanotic lips are generally a manifestation of peripheral cyanosis. The same is true for distal extremity cyanosis. On rare occasions, peripheral cyanosis of the extremities may extend to the arms and thighs. The condition may last for several months and is entirely benign. Some think this condition is caused by vasomotor instability. Regardless, simple in-hospital or office observation of the buccal mucosa while the baby cries usually distinguishes whether the cyanosis is central. The mucosa becomes cyanotic only with central cyanosis.

The discovery of a heart murmur in a newborn should not be a cause for alarm. A rule of further help to practitioners is to "judge all heart murmurs in the company they keep." A newborn with a systolic murmur who has none of the historical clues listed by Moss, is well formed, has no associated physical findings, and feeds well should be regarded as having a normal murmur. The baby in question needs only careful cardiac examinations in the course of a well-baby-care program. An echocardiogram is not necessary. An electrocardiogram and chest x-ray film are also of little help. More than half of all normal babies will have a heart murmur whereas fewer than 1 in 100 will have a heart defect. Pediatric cardiac consultation likewise may be postponed, for many of these murmurs will resolve.

The pitfalls of mistaking a murmur as normal when in fact a heart disorder is present are minimal in an overtly well infant, provided pulmonary hypertension or a hypertrophic cardiomyopathy is not present. The former can lead to hypertensive pulmonary vascular disease, an inoperable state, and the latter to sudden death, although usually not until school age. Pulmonary hypertension is marked by a loud second component of the second heart sound (loud P_2). A loud P_2 is normal in a newborn, but not after the first few weeks. The presence of a left parasternal impulse (right ventricular heave) in an infant with a loud P_2 should alert the practitioner to the possibility of pulmonary hypertension. Cardiac consultation would then be indicated. Should a mild or moderate heart defect without pulmonary hypertension be missed in early life, it will generally become clear on subsequent examinations and not be a cause of grief.

In a similar vein, when a child is discovered to have a murmur, the same rule of judging the murmur's sound in the context of associated historical and physical findings, particularly a normal growth pattern, needs to be applied. Again, the vast majority will be found to be normal.[2] An especially valuable point to remember is that normal murmurs tend to be short; that is, they end well before the second heart sound. A sound-free "space" may be heard just before the second sound, which is in itself normally split and not loud. Of course, this does not apply to the venous hum so well described by Moss. I would like to advocate that murmurs not associated with heart disease be labeled "normal" and cou-